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| EXAMINER | |
|---|---|
| FORD, VANESSA L | |

| ART UNIT | PAPER NUMBER |
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| 1645 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/018,373 | BIGALKE ET AL. | |
| | Examiner | Art Unit | |
| | Vanessa L. Ford | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *11-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed January 24, 2007.

### *Rejection Withdrawn*

2. In view of Applicant's remarks the rejection of claims 11-18 under 35 U. S.C. 112, second paragraph, pages 6-10, paragraph 6 of the previous Office action is withdrawn.

### *Rejections Maintained*

3. The rejection under 35 U.S.C. 112 first paragraph is maintained for claims 11-18 for the reasons set forth on pages 3-6 paragraph 3 of the previous Office Action. The rejection as set forth in the previous Office action reiterated below:

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

The claims are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a human or animal with cosmetic conditions, dystonia or a nervous system disorder treatable with a botulinum toxin neurotoxin comprising administering a 145 to 200 units of pure botulinum toxin to the human or animal a botulinum neurotoxin from *Clostridium botulinum* of Type A, B, C, D, E, F or G or a mixture of two or more botulinum neurotoxins, wherein the neurotoxins or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes does not enable administering doses of about 2500 units and above of botulinum toxin in a

method for treating a human with cosmetic condition, dystonia or a nervous system disorder treatable with a botulinum toxin neurotoxin.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It should be noted that the instantly claimed invention encompasses all serotypes of botulinum toxins, at any dosage as well as encompassing botulinum toxins prepared by any manufacture. The specification provides working examples that disclose a method of treating spasmodic torticollis and cerebral palsy comprising administering to a patient 145 units and 200 units, respectively (Examples 7-8).

The instant specification has failed to provide enablement for cosmetic conditions, dystonia or a nervous system disorder treatable with a botulinum toxin neurotoxin comprising administering amounts of pure botulinum toxin ranging from 2500 units and above) to the human.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

The state of the art regarding botulinum toxin administration to subjects (humans) is cited below.

Gil et al *(U.S. Patent No. 6,787,517 published September 7, 2004)* teach that botulinum toxin is the most lethal natural biological agent known to man and has a very potent $LD_{50}$ (column 2). Gil et al teach that a specific dose of a toxin that would be lethal to 50% of the population of a certain species of an animal is called the $LD_{50}$ (column 2). Gil et al teach that the estimated $LD_{50}$ of botulinum toxin A (available from Allergan, Inc., BOTOX®) in humans is about 150,000 picograms or about 3000 units (column 2). Carruthers et al *(U.S. Patent No. 6,358, 917 B1 published March 19, 2002)* teach that botulinum toxin (BTX) is administered in units (column 3). Carruthers et al teach that "unit equivalents" is an amount of botulinum toxin which is equivalent to standard units of botulinum toxin A (column 3). Carruthers et al teach that a standard unit of BTX-A is defined as the $L_{50}$ for female Swiss Webster mice weighing 18-20 grams (column 3). Carruthers et al teach that the estimated human $LD_{50}$ (for a 70-kg person is 40 units/kg or about 2500-3000 units (column 3).

It should be noted that the instant claims do not recite any particular dosage. The prior art has taught that administering 2500-3000 units of botulinum toxin would result in death to a human patient. Thus, the instant specification has failed to teach the skilled artisan to make and use the claimed invention. It should be noted that *Webster's II New Riverside University Dictionary, The Riverside Publishing Company, 1984* defines the word "treat" as a matter of giving medical aid. The skilled artisan would conclude that administering a compound to a patient the would result in death would not be a defined as treating the patient. Thus, it would require guidance to determine the dosages the skilled artisan could administer to a patient to practice (make and use) the claimed

method. Therefore, the instant specification has failed to teach how to make and use the invention commensurate in scope with these claims.

In view of all of the above, Applicant has not satisfied the requirements as set forth under 35 U.S.C. 112 first paragraph.

Applicant's Arguments

Applicant urges that urges that the legal standard for enablement is whether one of average skill in the art could make or use the invention from the disclosure of the instant specification coupled with the information known in the art without undue experimentation. The current understanding of the art is evidenced by Shelly et al, Keen et al, Benedetto, Aoki, Greene et al and Borodic et al. Applicant urges that the specification provides examples for treatment of individuals which dosage is commensurate with dosages disclosed in the prior art for treatment of conditions treatable with botulinum neurotoxin.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed January 24, 2007 have been fully considered but they are not persuasive. It is the Office position that Applicant is claiming a method that broadly encompasses any dosage of botulinum toxin. As mentioned by Applicant references such as Shelly et al, Keen et al, Benedetto, Aoki, and Borodic et al teach the state of the art regarding using the botulinum toxin complex that includes complexing proteins (botulinum toxin type A or BOTOX®). Green et al teach purified botulinum toxin which is free of complexing proteins. The instant specification has only enabled the administering to patients 145 units and 200 units, respectively (Examples 7-8 of the instant specification). Thus, it would require guidance to determine what other

dosages of purified botulinum toxin (without complexing proteins) the skilled artisan could administer to a patient to practice (make and use) the claimed method. Therefore, the instant specification has failed to teach how to make and use the invention commensurate in scope with these claims.

In view of all of the above this rejection is maintained.

4. The rejection under 35 U.S.C. 102(b) is maintained for claims 16-18 for the reasons set forth on pages 6-7 paragraph 5 of the previous Office Action. The rejection as set forth in the previous Office action reiterated below:

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection was on the grounds that Green et al teach a method of treating patients (humans) with torticollis with immunity to botulinum toxin type A (see the Abstract and the Title). Green et al teach that patients that have an immunity to botulinum toxin A were successfully treated with botulinum toxin F (see the Abstract and page 480). Green et al teach that the botulinum toxin F administered to patients was purified (page 480). Green et al anticipate the claimed invention.

Applicant's Arguments

Applicant urges that Greene et al teach the use of botulinum type F complex and not a botulinum toxin that is free from complexing proteins as recited in the claims. Applicant urges the purified botulinum toxin type F is not a botulinum toxin that is free from complexing proteins.

Examiner Response to Applicant's Arguments

Applicant's arguments filed January 24, 2007 have been fully considered but they are not persuasive. Green et al teach purified botulinum toxin type F. Applicant has not provided any evidence to suggest that the purified botulinum toxin type F as taught by Green et al includes complexing proteins. Therefore, this rejection is maintained.

5. The rejection under 35 U.S.C. 103(a) is maintained for claims 11-12 and 14-15 for the reasons set forth on pages 8-9 paragraph 6 of the previous Office Action. The rejection as set forth in the previous Office action reiterated below:

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection was on the grounds that Green et al teach a method of treating patients (humans) with torticollis with immunity to botulinum toxin type A (see the Abstract and the Title). Green et al teach that patients that have an immunity to botulinum toxin A were successfully treated with botulinum toxin F (see the Abstract and

page 480). Green et al teach that the botulinum toxin F administered to patients was purified (page 480).

Green et al do not teach treatment of cosmetic conditions.

Carruthers et al teach that botulinum neurotoxin type A (botulinum A exotoxin) can be used for cosmetic conditions such as glabellar wrinkles or lines, Crow's feet, horizontal forehead lines, neck lines , mental creases , melolabial folds and facial asymmetry (pages 216-230). Carruthers et al suggest that other botulinum neurotoxins can be used as alternative treatments for individuals who have developed antibodies to botulinum toxin type A and have become non-response to that treatment (page 208).

It would have been *prima facie* obvious at the time the invention was made to administer purified botulinum toxin type F to patients that have developed neutralizing antibodies to botulinum neurotoxin type A and are nonresponsive to botulinum neurotoxin A therapy because Carruthers et al suggest that other botulinum neurotoxins can be used as alternative treatments for individuals who have developed antibodies to botulinum toxin type A and Green et al has demonstrated that patients that are non-responsive to treatment with botulinum neurotoxin A are responsive to treatment with purified botulinum neurotoxin type F. It would be expected barring evidence to the contrary, that botulinum toxin neurotoxin A can be used as an alternative to treat patient that have immunity to botulinum neurotoxin A therapy. The combination of prior art references teach the claimed invention.

Applicant's Arguments

Applicant urges that Green et al disclose botulinum toxin type F complex and not a purified botulinum toxin type F that is free from complexing proteins. Applicant urges that the prior art do not teach or suggest all of the instant claim limitations which is a requirement for a finding of prima facie obviousness. Applicant urges that Carruthers et al do disclose or suggest a neurotoxin free from complexing proteins.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed January 24, 2007 have been fully considered but they are not persuasive.

It is the Office's position that Applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited

and relied upon references which make up the state of the art with respect to the claimed invention. In response to applicant's argument regarding a case of prima facie obviousness, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Green et al teach a method of administering purified botulinum toxin type F (without complexing proteins) to a patient that has developed neutralizing antibodies to botulinum toxin type A (includes complexing proteins). Carruthers et al teach that botulinum toxin type A (including complexing proteins) can be used to treat cosmetic conditions such as wrinkles and facial lines. One would be motivated to used purified botulinum toxin type F to treat patients that have developed antibodies against botulinum toxin A (including complexing proteins) because Green et al has demonstrated that purified botulinum toxin F is a safe alternative to using botulinum toxin type A (including complexing proteins). There is nothing on the record to teach or suggest that the purified botulinum toxin type F as disclosed by Green et al includes complexing proteins. Therefore, this rejection is maintained.

6. The rejection under 35 U.S.C. 103(a) is maintained for claim 13 for the reasons set forth on pages 10-11 paragraph 7 of the previous Office Action. The rejection as set forth in the previous Office action reiterated below:

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection was on the grounds the teachings of Green et al and Carruthers et al have been described previously.

Green et al and Carruthers et al do not teach hyperhidrosis.

Shelley et al teach that palmar hyperhidrosis can cause serious social, psychologic and occupational problems (page 227). Shelley et al teach that botulinum toxin can be as safe and effective treatment for palmar hyperhidrosis (See the Abstract).

It would have been *prima facie* obvious at the time the invention was made to administer purified botulinum toxin type F to patients that have developed neutralizing antibodies to botulinum neurotoxin type A and are nonresponsive to botulinum neurotoxin A therapy as taught by Green et al and Carruthers et al because Carruthers et al suggest that other botulinum neurotoxins can be used as alternative treatments for individuals who have developed antibodies to botulinum toxin type A and Green et al has demonstrated that patients that are non-responsive to treatment with botulinum neurotoxin A are responsive to treatment with purified botulinum neurotoxin type F. It would be expected barring evidence to the contrary, that botulinum toxin neurotoxin F can be used as an alternative to treat patients that have hyperhidrosis that have immunity to botulinum neurotoxin A therapy. The combination of prior art references teach the claimed invention.

Applicant's Arguments

Applicant urges that Green et al disclose botulinum toxin type F complex and not a purified botulinum toxin type F that is free from complexing proteins. Applicant urges that the prior art do not teach or suggest all of the instant claim limitations which is a

requirement for a finding of prima facie obviousness. Applicant urges that Carruthers et al disclose or suggest a neurotoxin free from complexing proteins. Applicant urges that Shelley et al has been added because it specifically teach botulinum toxin therapy for hyperhidrosis.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed January 24, 2007 have been fully considered but they are not persuasive.

It is the Office's position that Applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. In response to applicant's argument regarding a case of prima facie obviousness, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Green et al teach a method of administering purified botulinum toxin type F (without complexing proteins) to a patient that has developed neutralizing antibodies to botulinum toxin type A (includes complexing proteins). Carruthers et al teach that botulinum toxin type A (including complexing proteins) can be used to treat cosmetic conditions such as wrinkles and facial lines. Shelley et al teach that botulinum toxin (including complexing

proteins) can be used to treat patients suffering from hyperhidrosis. One would be motivated to used purified botulinum toxin type F to treat patients that have developed antibodies against botulinum toxin A (including complexing proteins) because Green et al has demonstrated that purified botulinum toxin F is a safe alternative to using botulinum toxin type A (including complexing proteins). There is nothing on the record to teach or suggest that the purified botulinum toxin type F as disclosed by Green et al includes complexing proteins. Therefore, this rejection is maintained.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Status of Claims***

8. No claims allowed.

***Conclusion***

9. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
April 24, 2007

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER